Embryonic stem cell-derived thymic epithelial cells

Grant Award Details

Embryonic stem cell-derived thymic epithelial cells

Grant Type: SEED Grant

Grant Number: RS1-00321

Investigator:

Name:	Kenneth Weinberg
Institution:	Stanford University
Type:	PI

Disease Focus: Immune Disease

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $628,793

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Progress Reports

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View Report

Grant Application Details

Application Title: Embryonic stem cell-derived thymic epithelial cells

Public Abstract: The function of the immune system throughout life is essential for protection from infections and cancer. T lymphocytes are white blood cells that choreograph the multiple responses that the body uses to control infection. T lymphocytes are produced in the thymus, a specialized organ located in the chest in front of the heart. The production of new T lymphocytes ("thymopoiesis") is abnormal in some children with genetic defects in the development of the thymus (DiGeorge syndrome [DGS]), but even in healthy people, thymic function declines with age. Thymic insufficiency, the decreased ability of the thymus to make new T lymphocytes, is a serious health problem. For example, if the T lymphocytes that have been previously made were to be destroyed by HIV infection, chemotherapy or radiation therapy, or hematopoietic stem cell transplantation, the restoration of immune function requires the production of new T lymphocytes to replace those that were lost. For this reason, adults with such conditions have poorer recovery of immune function than children and the elderly have increasing risk of severe infection with age. For example, 10-40% of the elderly do not respond to annual influenza vaccination and as many as 50-100,000 may die of influenza annually. Thymic insufficiency is due to injury or death of cells called thymic epithelial cells (TEC). TEC resemble skin cells but produce a number of proteins such as interleukin-7 (IL-7) needed by developing T lymphocytes in the thymus ("thymocytes"). Like skin cells, TEC become more fragile and easily injured with age. Also like skin cells, TEC are destroyed by chemotherapy and radiation therapy. Clinical efforts to restore thymopoiesis in patients with HIV infection by transplantation of thymic tissue from unrelated donors have not been successful because of rejection of the transplanted tissue. Experimental efforts to correct the problem of decreased thymopoiesis have included attempts to replace TEC functions by injections of IL-7 or other cells that make IL-7; or to regenerate TEC by the injection of keratinocyte growth factor (KGF), a protein that stimulates the growth of TEC.Human embryonic stem cells (hESC) are a potential source of replacement TEC that could be used to regenerate the immune system in people whose pool of T lymphocytes has been decreased, e.g., the elderly, or those with HIV or cancer. In order to implement such a strategy, research on how to control the development of TEC from hESC are necessary. The proposed studies will test how certain growth factors and genes such as those defective in DGS control the development of TEC from hESC. In addition, the studies will develop model systems in mice for testing the ability of TEC to be transplanted, a necessary scientific tool for the assessment of future therapies that will use TEC progenitors to restore immune function.

Statement of Benefit to California:	The research is aimed at understanding the generation of TEC in an effort to ultimately develop clinical strategies for thymic regeneration to treat thymic insufficiency. Thymic insufficiency occurs as both primary defects of TEC development and more commonly as acquired defects in TEC maintenance. Thymic insufficiency was first recognized in children with the rare DiGeorge syndrome (DGS), in which thymic hypoplasia occurs. More recent studies have shown that age-related thymic insufficiency is a common problem that progresses, and influences the outcome of many diseases. If an individual has a condition that results in destruction or increased turnover of mature T lymphocytes, their health will ultimately depend on the ability of the thymus to produce new T lymphocytes. An example is HIV infection, in which immunological recovery depends not just on the efficacy of anti-retroviral therapy to decrease the viral burden and T lymphocyte destruction, but also on the ability of the thymus to produce new T lymphocytes to replace those that were previously destroyed. The ability to do so is inversely related to age. Similar age-related thymic insufficiency occurs in recipients of high dose chemotherapy for cancer and in recipients of hematopoietic stem cell transplants (HSCT). Probably the largest group of individuals who are affected by thymic insufficiency are the elderly. There is evidence that the declining immune responsiveness of the elderly is a serious problem, particularly as it relates to common respiratory virus infections, such as influenza and respiratory syncytial virus, which together kill >50,000 Americans each year.In discussing the relevance of the studies to California, it must be recognized that this CIRM Seed Grant is aimed at a set of basic questions that will not immediately translate into health benefits. Nevertheless, it is possible to make estimates of how many individuals have conditions that this work is directly related to. For example, DGS is thought to affect 5% of all children with congenital heart disease and 20-25% of those with severe CHD, especially those with conotruncal abnormalities. Using the estimated 500-600,000 births per year (http://cgi.rand.org) and an incidence of 0.4% of severe CHD, there are about 500-600 births of children with DGS in California per year. Based on CDC serosurveillance data, tens of thousands of Californians are HIV infected and tens of thousands others receive either intensive chemotherapy or HSCT annually. Finally, the 2000 census showed approximately 3.5 million Californians over the age of 65 (http://www.census.gov/census2000/states/ca.html). Thus, the research proposed in this grant is likely to be directly related to the health of millions of individuals in California as well as having large impact on health economics.